REMARKS

I. Status of the claims

Of claims 38-71, claims 44-71 have been withdrawn from consideration. Claims 38-43 stand rejected. No claims are amended in this response.

II. Affirmation of Election

Applicants affirm their election, with traverse, of the subject matter of claims 38-43 for prosecution on the merits.

III. Rejection Under 35 U.S.C. § 103(a)

Claims 38-43 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 03/082831 ("Bradbury") in combination with Patani, *Chem. Rev.* 96:3147-3176 (1996). The Office Action asserts that one having ordinary skill in the art, at the time this invention was made, would have been motivated to combine the teachings of Bradbury and Patani and to methylate the acetamido substituent on the 1-position (nitrogen) of the piperidine ring of Bradbury's Example 11. Office Action at p. 6. Applicants respectfully disagree and traverse that rejection.

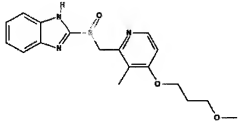
A. No Position Isomers

Initially, Applicants note that the Office's discussion about position isomers at pages 5-6 of the Office Action is factually irrelevant. Bradbury's Example 11 and the presently claimed compound are not position isomers and, therefore, not one of the 20 legal cases cited by the Office is controlling, let alone relevant.

B. Example 11 is Not the Lead Compound for § 103(a) Purposes

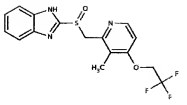
Post-KSR, a prima facie case of obviousness for a chemical compound begins with the reasoned identification of a lead compound. *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, *13 (Fed. Cir., July 21, 2008). In *Eisai,* the plaintiffs' patent claimed rabeprazole and its salts.

Rabeprazole



The main reference cited against the claims was a patent claiming lansoprazole, differing structurally from rabeprazole only at the 4-position on the pyridine ring - where the claimed rabeprazole had a methoxypropoxy group (-$OCH_2CH_2CH_2OCH_3$), as shown above, the prior art lansoprazole had a trifluoroethoxy group (-OCH_2CF_3), as shown below.

Lansoprazole

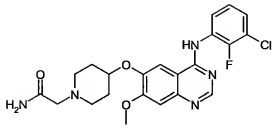


The argument was that one of ordinary skill in the art would have been motivated to select lansoprazole as a lead compound, and would have modified that molecule to arrive at rabeprazole. The court rejected that argument, focusing on the lack of any reason to select lansoprazole as a lead compound. As will now be explained, just as in the *Eisai* case, there is no reason of record for selecting Example 11 as the lead compound.

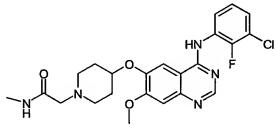
1. There is No Rationale for Selecting Example 11

In the present application, the Office proposes that one of ordinary skill in the art would have selected Bradbury's Example 11, shown below, as the lead compound or, in other words, the closest prior art. However, the Office provides no rationale for the selection of Example 11, chemically named as 6-{[1-(carbamoylmethyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline. The Office also provides no reason why one skilled in the art would have modified Example 11 by replacing H with CH_3 to arrive at the presently claimed 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoyl-methyl) piperidin-4-yl]-oxy}quinazoline, also shown below.

Bradbury's Example 11



4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl) piperidin-4-yl]-oxy}quinazoline (part of the present claims)



More specifically, the Office provides no rationale for selecting Example 11 of Bradbury as a lead compound. To be sure, Bradbury discloses at page 66, lines 21-26, two preferred compounds, one of which is Example 11 and the other of which is 4-(3-chloro-2-fluoroanilino)-6-{[1-(methylsulfonyl)piperidin-4-yl]oxy}-7-methoxyquinazoline. Nowhere, however, does Bradbury disclose any particular preference for Example 11 over the "methylsulfonyl" compound. In other words, there is no rationale for selecting Example 11 as the lead compound over the "methylsulfonyl" compound.

And that list of two preferred compounds is not the only list of preferred compounds. In fact, Bradbury discloses two additional lists of preferred compounds. One of those lists includes 13 preferred compounds, as set forth in the paragraph

bridging pp. 66-67. Example 11 does not even appear in that list. And there is no reason established why one skilled in the art would select Example 11 as the lead compound over any of the 13 preferred compounds in that second list.

Moreover, from p. 67, line 16 to page 70, line 20, there is yet a third list of preferred compounds, this time numbering almost 60. Example 11 is nowhere to be found in that third list. And there is no reason established why one skilled in the art would select Example 11 as the lead compound over any of the almost 60 preferred compounds in that third list.

So, in sum, Example 11 is merely one of the 67 Examples disclosed in Bradbury. And there is absolutely no rationale of record for picking Example 11 as the lead compound over the array of other preferred compounds, particularly since Bradbury does not present any experimental or biological data for Example 11. In other words, nothing in Bradbury would have led the skilled artisan to Example 11 as the lead compound.

Pure hindsight dictated the Office's selection of Example 11. And hindsight remains as improper after *KSR* as before. *KSR Int'l Co. v. TeleFlex Inc.*, 127 S.Ct. 1727, 1742 (2007).

2. No Rationale to Modify Ex. 11 to Achieve Claims

Assume *arguendo* solely for purposes of argument that one skilled in the art had been motivated to select Bradbury's Example 11 as a lead compound. In that case, she

would have had no reason to modify that compound in the manner proposed by the Office. As will now be discussed, Patani provides no such reason.

a. Patani does not discuss anilinoquinazolines

The Office relies on Patani to teach "the relationship between $-CH_3$ groups and -H atoms as monovalent bioisosteres, which exert similar biological activity [p. 3148; column 1], via a direct adaptation of Grimm's Hydride Displacement Law [p. 3152, section A4; p. 3153 - column 1, ¶ 2; p. 3163, Table 12 - column 2]." Office Action at page 4. That reliance is not only misplaced, but constitutes prohibited hindsight. *KSR Int'l Co. v. TeleFlex Inc.*, 127 S.Ct. 1727, 1742 (2007).

Not one of the compounds of Patani is an anilinoquinazoline, and thus Patani sheds no light on whether a hydrogen and a methyl group would be considered bioisosteres in that very different chemical and electronic environment of the claimed anilinoquinazolines. The Office has furthermore not provided any basis upon which the skilled artisan could bridge that gap.

b. Patani does not establish bioisosterism between $-CH_3$ groups and -H atoms

Patani also does not establish equivalence between $-CH_3$ groups and -H atoms as monovalent bioisosteres on any molecules. Patani reports that Langmuir in 1919 came up with groups of isosteres based on similarities of various physicochemical properties. In Table 1, p. 3148, Langmuir's conclusions are reported. H^- is placed in Group 1, but CH_4 is placed in Group 9. So Langmuir did not place hydrogen and methyl

in the same group of isosteres. Patani's disclosure of Langmuir thus provides no support for bioisosterism between methyl and hydrogen.

Moreover, Patani reports that in 1925, Grimm, relied on by the Office, extended the concept of isosteres. In Table 2, p. 3148, Patani reports Grimm's sets of isosteres. Methyl appears in a group with amino, hydroxyl, and fluoro, but hydrogen is not mentioned at all, let alone in that group of amino, hydroxyl, and fluoro. So Patani's disclosure of Grimm provides no support for bioisosterism between methyl and hydrogen.

With respect to bioisosterism, Patani explains that, as initially defined by Friedman, bioisosteres were to include all atoms and molecules that (1) fit the broadest definition of isosteres and (2) have a similar type of biological activity. However, as explained above, there is no evidence in Patani that hydrogen and methyl are isosteres. Thus, Patani's disclosure of Friedman's definition provides no support for bioisosterism between methyl and hydrogen.

Patani also provides, at p. 3148, Burger's definition that bioisosteres are compounds or groups that possess near equal molecular shapes and volumes and approximately the same distribution of electrons, and exhibit similar properties. There is no evidence of record that hydrogen and methyl meet any of those criteria. That is another reason why Patani establishes no bioisosterism between the hydrogen and methyl substitutents.

Nor does Patani report any data establishing bioisosterism. At p. 3153, col. 1, Table 11, Patani reports a comparison of three alleged N-(substituted-3-pyridyl)-N'-alkylthioureas substituted at the 6-position with an amine group, a methyl group, or a

chlorine atom. That portion of Patani explains that (emphasis added) "[t]he methyl group, which has lower electronegativity [than the other groups], elicited a weaker pharmacological response, suggesting an additional correlation between activity and physicochemical property" is required for establishing bioisosterism.

Hence, it is Patani's conclusion that an important question to ask regarding bioisosterism is whether two substituents under consideration for classification as bioisosteres have correlated activity and physiochemical properties. But there is no evidence in Patani that hydrogen and methyl have similar physicochemical properties. Patani, consequently, provides no evidence that hydrogen and methyl meet the similar physiochemical property prong of Patani's view of bioisosterism.

Patani, moreover, reports at p. 3148, left column, that the ability of a group of isosteres to elicit similar biological activity has been attributed to common physiochemical properties. But since Patani reported no evidence to establish that hydrogen and methyl have common physiochemical properties, there would be no prediction of bioisosterism between the two.

To be sure, Patani states in the title of section 4, at page 3152, left hand column: "fluorine and hydroxyl, amino or methyl groups as replacements for hydrogen. . . . " One might read that as an assertion of bioisosterism between hydrogen and methyl. But as noted above, Patani failed to establish isosterism or common physiochemical properties between methyl and hydrogen and, thus, by his own admission, failed to establish bioisosterism between methyl and hydrogen.

For those reasons, nothing that the Office has provided would have given one of ordinary skill in the art any reason to choose Example 11 as a lead compound, much less to replace a hydrogen atom with a methyl group.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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